Background Information on SARS-CoV-2 Replication and Potential Role of Hydroxychloroquine

SARS-CoV-2 Viral Replication

The 2019 novel coronavirus SARS-CoV-2 and COVID-19, the illness it causes, were first reported to the World Health Organization China Country Office in December 2019. SARS-CoV-2 is genetically related to SARS-CoV, which caused an outbreak in 2002-2003 but was effectively contained. Defining the mechanism of viral replication for SARS-CoV-2 and how it may be interrupted are among the primary early objectives regarding COVID-19. A study of 14 patients from Wuhan indicates the nucleic acid shedding pattern of SARS-CoV-2 is different than SARS-CoV and more closely resembles influenza.[1] In the study, higher SARS-CoV-2 viral loads were detected soon after symptom onset, with higher loads detected in the nose than in the throat. Also, the viral load was similar in both symptomatic and asymptomatic patients, suggesting transmission can occur early after infection. This diverges from SARS-CoV shedding and transmission patterns which indicates patient identification and management strategies will also vary.

The level and duration of infectious viral replication are important factors in recognizing risk of transmission, as well as informing the management of infected patients. As described above, viral loads can be detected and transmission can occur prior to patients showing symptoms. Most laboratories and identification instruments use viral RNA tests as a marker for SARS-CoV-2, as RNA detection is more sensitive than virus isolation. In a study of 191 patients in China, SARS-CoV-2 RNA persisted for a median of 20 days in surviving patients (until death in non-survivors).[2] The period of detectable RNA may affect the duration of antiviral treatment, as well as isolation times. For instance, in hospitalized patients with avian influenza A infection, prolonged viral shedding was associated with a fatal outcome, and delaying antiviral treatment was an independent risk factor for prolonged virus detection.[3] Given similar viral shedding patterns, it is reasonable that certain antiviral treatments can shorten SARS-CoV-2 viral shedding and improve outcomes in COVID-19.

To understand the mechanism of potential antiviral treatment options it is important to discuss the fundamental properties of SARS-CoV-2. SARS-CoV-2 is an enveloped, positive strand RNA virus and contains four structural proteins: spike (S), envelope, membrane and nucleocapsid.[4] The spike protein is a viral fusion protein that promotes attachment and fusion of the viral membrane to the host cell for virus entry. Once attached, the S protein is the cleaved by host proteases to facilitate viral entry. Of note, the S protein is also expressed on the infected cell surface and responsible for syncytial formation, which is essentially the fusion of an infected cell with multiple uninfected neighboring cells. Another component of SARS-CoV-2 mechanism of cell entry is utilization of the cell surface receptor ACE2, which is expressed in the lungs and other organs. Binding to ACE2 may trigger the conformational changes and cleavage of the S protein needed for viral envelope entry.

Chloroquine/Hydroxychloroquine: Antiviral Mechanism of Action

It is important to consider how chloroquine/hydroxychloroquine interfere with the viral process given the rapid replication to high viral loads and increased risk of transmission. Chloroquine (and hydroxychloroquine) has been proposed as a potential treatment option, as it has previously demonstrated potent inhibition of most coronaviruses, including SARS-CoV.[5]

There is substantial evidence indicating chloroquine has antiviral activity against RNA viruses in vitro, but these results have not always been reproducible in clinical trials depending on the disease, chloroquine dose, and duration of treatment.[5] Numerous different antiviral processes have been attributed to chloroquine. Several of these processes have specific plausible justifications for chloroquine's antiviral activity in SARS-CoV-2, but have not been fully explored.

One antiviral mechanism for chloroquine is potential interference with the virus ACE2 receptor, which prevents SARS-CoV-2 from binding to host cells and may also prevent the increased expression of ACE2 by the virus. Specifically, through chloroquine's interaction with ACE2, it disrupts cleavage of SARS-CoV-2 spike (S) protein (which is needed to attach to host cells) by preventing acidification of host cell proteases. Another chloroquine antiviral mechanism is inhibiting the process of SARS-CoV-2 crosstalk to the host cell via MAP kinase. The M protein, responsible for viral repackaging and budding, is another plausible target for chloroquine disruption. Finally, the production of proinflammatory cytokines activated by SARS-CoV-2 may be indirectly blunted by chloroquine.

In summary, chloroquine and hydroxychloroquine change the pH at the surface of the cell membrane and thus, inhibit the fusion of the virus to the cell membrane. The drugs also inhibit nucleic acid replication, glycosylation of viral receptor proteins, virus assembly, new virus particle transport and release, and have other broad immunomodulatory effects.[6] It is easy to see why hydroxychloroquine is being comprehensively investigated given the numerous mechanisms and different sites of action in the SARS-CoV-2 infectious process.

Chloroquine/Hydroxychloroquine: Potential Role in Pre-exposure Prophylaxis

The mechanisms of action for chloroquine/hydroxychloroquine demonstrate how it could be used not only for the treatment of acute COVID-19 infection, but also for prophylaxis. Chloroquine and hydroxychloroquine can interfere with the initial binding of SARS-CoV-2 to host cells which may prevent the replication needed to develop symptoms and prevent high viral loads ideal for transmission. For hydroxychloroquine, in vitro pre-treatment demonstrated viral inhibitory effects, as further discussed in the clinical trials section.[6] Both chloroquine and hydroxychloroquine can help mitigate a potential cytokine storm in COVID-19 patients which is another rationale for prophylactic use in patients who are at risk for a severe or critically ill disease course (e.g. baseline respiratory disease, immunosuppressed, geriatric).[6]

References

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